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PHYSIOLOGICAL STUDIES IN CONGENITAL HEART DISEASE*

I. Procedures

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Recent studies which led to the surgical treatment of the group of congenital heart disease with cyanosis, have stressed the physiological importance of diminished rate of pulmonary blood flow in the production of anoxemia (1). Varying types of congenital malformations of the heart with reduced volume of circulation through the lungs have been described. These include, first, cases with pulmonary atresia or stenosis, alone or in combination with other malformations to form the "tetralogy of Fallot"; second, those with a single ventricle in which the pulmonary artery arises from the rudimentary outlet chamber; and third, cases with truncus arteriosus, in which the circulation to the lungs courses through the bronchial arteries (1). It seemed of importance to study, quantitatively, the changes in pulmonary blood flow in these conditions in order to correlate this primary abnormality with accompanying hemodynamic and respiratory alterations. Furthermore, the severity and prolonged duration of anoxemia in individuals with reduced pulmonary blood flow provided an opportunity to investigate certain aspects of physiological adaptation to reduced arterial oxygen saturation. Finally, the practical significance of recognizing pulmonary stenosis and atresia preoperatively has made it advisable to study the diagnostic value of the physiological tests outlined below.

This communication deals with technical procedures employed in the study of congenital heart diseases belonging to the cyanotic group. Separate reports will be published which deal with preoperative findings in patients with reduced pulmonary blood flow, with postoperative findings in the same group, and with investigations in individuals with increased circulation through the lungs.

* This study was supported by a grant from the Commonwealth Fund.

The following procedures were employed: measurement of oxygen capacity and oxygen saturation of arterial blood; measurement of the oxygen and carbon dioxide content of blood obtained from peripheral arteries and from the cardiac chambers accessible to catheterization via the right side of the heart; determination of the rates of oxygen consumption and carbon dioxide elimination by indirect calorimetry; gas analyses of respiratory air under various conditions; and, finally, recording of arterial and intracardiac pressure curves.

Some of the data obtained were used for calculation of the blood flow through the lungs and the systemic circulation, and for estimation of the volume and direction of extra- and intracardiac shunts. These calculations in some instances involve assumptions which are of doubtful validity and it is realized that the resulting figures should be looked upon as no more than approximations. The actual data upon which the calculations have been based will be presented in the following papers. The succeeding paragraphs of this paper deal with the theoretical basis of the calculations and indicate some of the sources of error.

Measurement of the circulation through the pulmonary artery and the systematic circulation: According to Fick (2), the output of the heart may be calculated with the formulae:

1. Cardiac output (ml. per min.)

$$= \frac{O_2 \text{ intake (ml. per min.)}}{O_2 \text{ content of arterial blood (vol. per cent)} - O_2 \text{ content of mixed venous blood (vol. per cent)}} \times 100$$

or

2. Cardiac output (ml. per min.)

$$= \frac{CO_2 \text{ output (ml. per min.)}}{CO_2 \text{ content of mixed venous blood (vol. per cent)} - CO_2 \text{ content of arterial blood (vol. per cent)}} \times 100$$

During recent years Cournand and associates developed methods which permit the direct application of these formulae to the determination of cardiac output in man (3a). Samples of mixed venous blood from the right auricle or ventricle are collected by catheterization of these chambers and arterial samples are secured by direct puncture

of a peripheral artery[1]. Blood gas values obtained by Cournand's methods provide valid figures for pulmonary blood flow only if the oxygen and carbon dioxide contents of peripheral arterial blood are identical with those in the pulmonary vein. In the majority of cardiac abnormalities, however, which were the subject of this investigation, admixture of blood resulted in arterial blood gas values which differed from those in the pulmonary vein. Consequently it was found necessary to derive values for oxygen and carbon dioxide concentrations of the pulmonary vein blood by indirect means. To accomplish this the following formula was employed:

3. O_2 content of pulmonary vein (vol. per cent) = percentage O_2 saturation of pulmonary vein $\times$ O_2 capacity (vol. per cent)

The percentage of oxygen saturation of the pulmonary vein blood was assumed to be 95 per cent. This represented an accepted value for normal individuals (4), and agreed with our analyses of pulmonary vein blood obtained through direct catheterization of that vessel in 4 cases with tetralogy of Fallot.

The carbon dioxide content of the pulmonary vein blood was derived from the alveolar concentration of this gas, the volume of the gas per 100 cc. of blood being obtained by plotting the tension on an oxygenated carbon dioxide absorption curve which was determined for each patient. The oxygen capacity was determined according to the method described in a subsequent paragraph.

The blood flow through the pulmonary artery was subsequently calculated with the equations:

4. Pulmonary artery flow (ml. per min.)

$$= \frac{O_2 \text{ intake (ml. per min.)}}{O_2 \text{ content of pulmonary vein (vol. per cent)} - O_2 \text{ content of pulmonary artery (vol. per cent)}} \times 100$$

[1] Formulae described in this paper include calculations of flows with both blood oxygen and carbon dioxide. In the succeeding reports, however, calculations based on blood carbon dioxide values will be omitted, since their accuracy has been found to be questionable (3b).

or

5. Pulmonary artery flow (ml. per min.)

$$= \frac{\text{CO}_2 \text{ output (ml. per min.)}}{\text{CO}_2 \text{ content of pulmonary artery (vol. per cent)} - \text{CO}_2 \text{ content of pulmonary vein (vol. per cent)}} \times 100$$

In normal individuals, sampling of blood from the pulmonary artery has been easily accomplished by catheterization (5). In the majority of patients with severe pulmonary stenosis, however, this procedure was impossible, since the catheter could not be passed through the narrowed lumen. In these cases gas values for right ventricular blood were substituted for those of the pulmonary artery. Large interventricular septal defects with shunting between the chambers made it probable that the concentration of blood gases in the right ventricle was not identical with that in the pulmonary artery, introducing an error in the estimation of pulmonary artery blood flow. A further difficulty in the calculation of the blood flow through the pulmonary artery by means of the Fick principle arose from the observation that some individuals, especially those belonging to the older age group, had developed a large collateral circulation to the lung as compensation for the pulmonary stenosis. In these cases, the quantity of oxygen consumed or of carbon dioxide released was too high in relation to the volume of blood which reached the alveolar epithelium via the pulmonary artery alone. This error in the calculation of pulmonary flow became greater as the ratio of collateral circulation to pulmonary artery flow increased. In pulmonary atresia, for instance, the total amount of oxygen diffusing through the alveolar epithelium was taken up by the pulmonary collaterals. In these cases, where pulmonary artery flow must be zero, values for pulmonary artery flow were obtained by calculation. This makes the recognition of pulmonary atresia impossible by the methods described above.[2]

[2] An attempt was made to overcome this difficulty in calculating pulmonary artery flow with formulae developed from mixing equations.

1. $$\frac{(\text{PACO}_2 \times \text{PAF}) + (\text{CCO}_2 \times \text{CF})}{\text{PAF} + \text{CF}} = \text{PCCO}_2$$

2. $$\text{PCF} = \text{PAF} + \text{CF}$$

These considerations made it evident that values estimated for the blood flow through the pulmonary artery in patients with tetralogy of Fallot and related conditions were approximations. They were, however, of sufficient accuracy to permit a preoperative diagnosis of pulmonary stenosis, although the degree of the stenosis could not be predicted with accuracy.

Measurement of systemic blood flow: The Fick principle was also applied in determining the blood flow through the systemic circulation. Because of the admixture of blood in hearts with interventricular septal defects, carbon dioxide and oxygen concentrations in right ventricular blood were not identical with true mixed venous blood. Although normally the blood entering the heart is not fully mixed until it reaches the right ventricle (6), right auricular samples had to be used in the calculation of systemic blood flow according to the formulae:

6. Systemic flow

$$= \frac{O_2 \text{ consumption (ml. per min.)}}{O_2 \text{ content of arterial blood (vol. per cent)} - O_2 \text{ content of right auricular blood (vol. per cent)}} \times 100$$

or

7. Systemic flow

$$= \frac{CO_2 \text{ production (ml. per min.)}}{CO_2 \text{ content of right auricular blood (vol. per cent)} - CO_2 \text{ content of arterial blood (vol. per cent)}} \times 100$$

Values for oxygen consumption and carbon dioxide production used in the above formulae refer to the oxygen consumed and carbon dioxide produced by the tissues. It can be assumed, however, that these values are identical with the oxygen uptake and carbon dioxide output in the lung.

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where $PACO_2$ = CO_2 content of pulmonary artery; PAF = Pulmonary artery flow; CCO_2 = CO_2 content of collateral circulation; CF = Collateral flow; $PCCO_2$ = CO_2 content of pulmonary capillary blood; PCF = Pulmonary capillary flow.

Equation 1 solves for PAF and CF in terms of each other. Then, by substituting in equation 2, the absolute values are obtained. These formulae permitted calculations of pulmonary artery flow without using values for oxygen consumption. However they were abandoned since they relied upon carbon dioxide values of doubtful accuracy.

The systemic flow calculated with formulae 6 and 7 represents only the blood flow through the systemic circulation; it does not include the flow through the pulmonary collaterals, which originate from systemic vessels and course to the lung. These pulmonary collaterals do not share in the unloading of oxygen or the uptake of carbon dioxide in the tissues and contribute nothing to the total oxygen consumption or carbon dioxide production. Consequently, the amount of blood which courses through the aortic valves during systole (the aortic output) represents the sum of systemic flow and collateral circulation to the lung.

Determination of the total volume of blood perfusing the lung (pulmonary capillary flow): Clinical findings frequently indicated that pulmonary stenosis was accompanied by large collateral circulation or by a persistent ductus arteriosus. Consequently it seemed of interest to determine the total volume of pulmonary blood flow in order to compare it with the blood flow through the pulmonary artery. Here the Fick principle could be applied only if the concentrations of blood gases entering and leaving the pulmonary capillary bed were known. These values could be estimated by indirect means only. For this purpose the pulmonary alveolar space was employed as an aerotonometer for carbon dioxide in order to determine the concentration of this gas in the blood as it entered the pulmonary capillaries. After various unsuccessful attempts to obtain equilibration through the use of rebreathing methods a procedure was adopted which combined in principle the methods of Christiansen, Douglas, and Haldane (7) and of Field and his co-workers (8). Three anesthesia bags were filled with carbon dioxide and oxygen mixtures from specially prepared storage tanks. Since the partial pressure of carbon dioxide in the pulmonary capillary blood ranged from 25 to 40 mm. of mercury, the carbon dioxide contents of the bags were approximately 4, 5, and 6 per cent of carbon dioxide respectively, the remaining volume being composed of oxygen. The small difference between the carbon dioxide contents of the bags was necessary because it was found that equilibration was impossible if the carbon dioxide tensions in any bag differed more than 2 per cent from those of pulmonary capillary blood. The total amount of gas in the bags was adjusted to conform to the vital capacity of the subject. After collection of expired air for measurement of the carbon

dioxide output the blood coming in contact with the pulmonary alveoli was equilibrated successively with the carbon dioxide of each bag. This was accomplished by requesting the patient to inhale the contents of the bag completely. After holding the gases in the lung for a period of 8 to 10 seconds, the equilibrated carbon dioxide mixture was exhaled into the bag by a forceful expiration. Special care was taken to assure maximal expiration in order to collect a representative sample of equilibrated lung air. If after analysis the final concentrations of carbon dioxide in the three bags were within .2 per cent of one another, it was assumed that equilibration had been reached. In several cases it was found necessary to re-equilibrate the bags several times, before their carbon dioxide contents reached satisfactory agreement. Alveolar air was then collected in order to determine the carbon dioxide content of pulmonary vein blood. This was accomplished by methods described later. To determine blood gas concentrations in volumes per cent the averaged final carbon dioxide tensions in the bags as well as the carbon dioxide tensions in the alveolar air were plotted on an oxygenated carbon dioxide *absorption* curve for the individual. Pulmonary capillary flow was then calculated according to the formula:

8. Pulmonary capillary flow (Total pulmonary blood flow) ml. per min.

$$= \frac{\text{CO}_2 \text{ output (ml. per minute)}}{\text{CO}_2 \text{ content of blood reaching alveoli (vol. per cent)} - \text{CO}_2 \text{ content of pulmonary vein blood (vol. per cent)}} \times 100$$

The principal source of error inherent in the determination of pulmonary capillary flow, by the method described above, lay in the possible occurrence of re-circulation of blood already in contact with the carbon dioxide in the bags (9). This could result in low calculated flows by raising the arteriovenous difference in formula 8. For this reason the results obtained with the method described above can only be accepted as approximations. The physiological and diagnostic value of this method, however, will become obvious in the suceeding papers.

Determination of shunts: Pulmonary capillary flow, as defined above, represented the amount of blood reaching the lung through the pulmonary artery and through collateral vessels. Consequently, the

measurement of total pulmonary artery and capillary flows permitted the determination of the volume flow through the collateral circulation to the lung by the following formula:

9. Collateral circulation to the lungs (ml. per minute) = pulmonary capillary flow (ml. per minute) − pulmonary artery flow (ml. per minute)

It has been impossible, with the methods described, to state whether or not the collateral circulation consists of a patent ductus or of a series of vessels originating in the aorta. Consequently, the sum total of the blood flowing to the lung through channels other than the pulmonary artery will be referred to as "collateral circulation" in the succeeding papers.

In cases of tetralogy of Fallot systemic flow exceeded that through the pulmonary artery, the difference between the two volume flows representing the shunt from the right ventricle through the interventricular septal defect or the overriding aorta. Therefore, it was possible to calculate the intracardiac shunt, "right to left.":

Formula 10: Intracardiac shunt (right to left) (ml. per minute) = volume of blood flow through the systemic circulation (ml. per minute) − volume of blood flow through pulmonary artery (ml. per minute)

Calculation of mixed venous pulmonary flow: It became evident that the volume of intracardiac right to left shunt rather than a decrease in pulmonary blood flow contributed to arterial unsaturation by preventing the contact of mixed venous blood with pulmonary epithelium. Formulae were therefore derived which permitted calculations of the amount of mixed venous blood perfusing the lung. Mixed venous pulmonary flow may be defined as the volume of blood which after its return to the right auricle, ultimately reaches the pulmonary alveoli. Since it is the only component of the circulating blood which becomes effectively oxygenated in the alveolar space it will be referred to as the "effective pulmonary blood flow".

11. Effective pulmonary blood flow (ml. per minute)

$$= \frac{O_2 \text{ consumption (ml. per min.)}}{O_2 \text{ content of pulmonary vein blood (vol. per cent)} - O_2 \text{ content of right auricle blood (vol. per cent)}} \times 100$$

12. Effective pulmonary blood flow (ml. per. min.)

$$= \frac{CO_2 \text{ output (ml. per min.)}}{CO_2 \text{ content of right auricle (vol. per cent)} - CO_2 \text{ content of pulmonary vein (vol. per cent)}} \times 100$$

The percentage of the total mixed venous blood which reaches the pulmonary epithelium was subsequently calculated with the following equation.

13. Percentage of total mixed venous blood reaching lung

$$= \frac{\text{effective pulmonary blood flow}}{\text{systemic blood flow}} \times 100$$

The relationship between pulmonary ventilation and gas exchange at rest and during exercise: The relationship between the breathing requirements (volume ventilation per minute) and the oxygen consumption and carbon dioxide production were investigated at rest and during a standard exercise identical with that described by Cournand and Richards (10). In several instances the breathing requirements were also studied during the period of recovery from exercise. The air expired during exercise was collected in a Douglas bag and its oxygen and carbon dioxide contents as well as its total volume were subsequently determined. Changes in minute volume during the recovery were recorded on an electrically driven kymograph which was connected with the bell of a Tissot spirometer. Arterial blood samples were taken preceding and immediately following the performance of the exercise.

Special techniques: Arterial and intracardiac pressures were optically recorded by means of a Hamilton manometer (11). Membranes of various sensitivities were used. Systemic mean pressures in the femoral artery were calculated by planimetric integration of the area under the pressure curve. The resistance in the systemic circulation (pheripheral resistance) was calculated by the formula of Aperia (12):

14. Peripheral resistance

$$= \frac{\text{mean systemic blood pressure}}{\text{flow in systemic circulation per second}} \times 1332$$

This formula represents the loss of pressure head in the peripheral circulation in absolute units, one unit representing one dyne /sec/cm^5.

The method of Haldane and Priestley was followed in collecting alveolar air samples (13). This procedure required a degree of cooperation from the subject which could not be obtained from younger children. In these individuals an automatic alveolar air sampler, first described by Smith and Heinbecker, was employed (14). Alveolar samples obtained with the automatic sampler agreed with those obtained by the method of Haldane and Priestley.

Carbon dioxide dissociation curves were constructed for the blood of each individual since the slope of the curve varied with the hemoglobin content of his blood. The method described by Peters was followed, the carbon dioxide contents and tensions being plotted against their logarithms (15). By following this procedure, linear oxygenated absorption curves were obtained from the points determined by equilibration of 5 cc. samples of blood with carbon dioxide concentrations of 4 and 7 per cent respectively, the remaining volume being composed of oxygen. Equilibration was carried out in a water bath at a temperature of 37°C. in tonometers of 450 cc. capacity.

All tests were performed under basal conditions without anesthesia. Carbon dioxide eliminated and oxygen consumed were determined by analysis of expired air collected in a Douglas bag, and measured in a Tissot spirometer. The gas analysis apparatus of Haldane, Boothby and Sandiford was used for the measurements of oxygen and carbon dioxide (16). All gas volumes were expressed in terms of dry gas at 760 mm. mercury and at 0 degrees Centrigrade.

Arterial blood was obtained by puncture of the brachial or femoral artery, after infiltration of the skin with 2 per cent procaine hydrochloride. The blood was collected under oil in syringes, each containing 2 mgs. sodium fluoride and 15 mgs. potassium oxalate per 10 cc. of blood. The oxygen capacity was determined by equilibration of 6 to 8 cc. of blood with room air for 20 minutes in tonometers of 450 cc. capacity. All blood gas analyses were carried out in the manometric apparatus of Van Slyke (17).

DISCUSSION

The preceding description of methods demonstrates the difficulties encountered in adapting the Fick principle to the study of the cir-

culation in individuals with malformations of the heart. This becomes especially apparent in the determination of the blood flow through the pulmonary artery. Interventricular admixture of venous with oxygenated blood results in concentrations of carbon dioxide and oxygen in the femoral artery which differ from those in the pulmonary vein. The tensions of these gases in the pulmonary vein, therefore, have to be calculated indirectly. The carbon dioxide content of the pulmonary vein is derived from the alveolar carbon dioxide tension, the oxygen content by multiplying the oxygen capacity of the blood by an assumed pulmonary vein saturation of 95 per cent. Results to be described in detail in subsequent publications confirm the validity of the latter assumption.

The failure to secure blood samples from the pulmonary artery of patients with severe pulmonary stenosis introduces a serious obstacle to the calculation of pulmonary artery blood flow. In these cases values for right ventricular blood must be substituted for those of the pulmonary artery, although in hearts with large interventricular shunts the gaseous content of right ventricular blood differs from that of the pulmonary artery. On the other hand, results, obtained in several cases with moderate stenosis in which the pulmonary artery could be intubated, demonstrate that the oxygen and carbon dioxide contents of the right ventricle and of the pulmonary artery differ only slightly if the catheter tip lies close to the pulmonary valve.

The development of a large collateral circulation to the lungs adds to the difficulties already encountered in the estimation of pulmonary artery blood flow. In these the quantity of oxygen consumed or of carbon dioxide released is too high in relation to the total minute volume perfusing the pulmonary artery. With an increase in the ratio of collateral circulation to pulmonary artery flow the accuracy of the formulae 4 and 5 diminishes. Consequently establishing the diagnosis of pulmonary atresia, in which pulmonary artery flow is zero, is impossible by these methods.

The foregoing discussion makes it apparent that values calculated for blood flow through the pulmonary artery can only be considered approximations. On the other hand, the values are sufficiently reliable to permit their use in the preoperative recognition of pulmonary stenosis. This is demonstrated by the fact that in all instances in

which evidence for reduced pulmonary artery flow was obtained by calculation, pulmonary stenosis was found during operation.

In contrast to the determination of pulmonary artery flow, the total amount of blood perfusing the lung (pulmonary capillary flow) can be calculated by indirect means only. One of the advantages of the indirect method lies in the fact that by comparing the results therefrom with those of catheterization of the pulmonary artery or right ventricle, the amount of collateral circulation to the lung can be estimated. This is of diagnostic importance since it is often difficult to distinguish on clinical or fluoroscopic grounds increased collateral circulation from increased pulmonary artery flow, which is found in Eisenmenger's syndrome. Furthermore, the amount of collateral circulation is of physiological importance as it represents one of the mechanisms by which the individual adapts to decreased pulmonary artery blood flow. Finally, following the Blalock operation, the determination of pulmonary capillary flow is of aid in the calculation of postoperative changes in the circulating volume of pulmonary blood.

The most important error in this method lies in a possible recirculation of carbon dioxide through the lung during equilibration a factor which results in abnormally high carbon dioxide values for blood entering the pulmonary capillaries and correspondingly low figures for pulminary capillary flow (9).

The determination of the volume of mixed venous pulmonary flow is of importance since it is the only component of the circulating blood which becomes effectively oxygenated in the pulmonary alveoli. Consequently this component is the "effective pulmonary blood flow," and determines the peripheral arterial oxygen saturation. Furthermore, postoperatively, the effect of the Blalock-Taussig operation can be calculated quantitatively by changes in the effective pulmonary flow.

Studies comparing the relationship of pulmonary ventilation and gas exchange during rest and exercise are undertaken primarily to investigate the ability of the individual to adjust his pulmonary flow to the increased respiratory demands of exercise. It has been shown that in normal individuals, the ratio of oxygen intake to the ventilatory volume rises during exercise, while the ratio of carbon dioxide output to liters of ventilation remains constant (10). In

individuals, however, in whom large areas of the lung during exercise are ventilated but not perfused, the ratio of oxygen consumption to respiratory volume decreases. If the circulation through the lung is very seriously impaired, then the ratio of carbon dioxide output to liters of ventilation also declines.

Analyses for respiratory gases in arterial blood at rest and during exercise have a similar purpose (10). In normal subjects a standard exercise is immediately followed by a slight decline in the oxygen saturation of arterial blood and an appreciable drop in carbon dioxide content. During exercise, when shunting of blood occurs by passage through vessels which fail to reach the alveolar epithelium, the arterial oxygen saturation decreases and the carbon dioxide content of arterial blood usually rises. Therefore, in the recognition and physiological interpretation of variations in the effective pulmonary blood flow, the exercise test represents a valuable supplement to the methods already described.

SUMMARY

Technical procedures employed in the study of congenital heart diseases belonging to the cyanotic group, have been described.

The physiological and diagnostic values of these procedures and their limitations are discussed.

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PHYSIOLOGICAL STUDIES IN CONGENITAL HEART DISEASE*

II. Results of Preoperative Studies in Patients with Tetralogy of Fallot

R. J. BING, L. D. VANDAM, AND F. D. GRAY, JR.

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In the first paper of this series the various physiological procedures employed in the investigation of congenital heart disease with cyanosis were described (1). This report deals with the results of preoperative studies on patients in whom clinical and physiological examinations indicated the presence of reduced pulmonary blood flow.

The Blood Flow Through the Pulmonary Artery, the Systemic Circulation, and the Volume of Intracardiac Shunt: The volume of blood flowing through the pulmonary arteries was calculated according to formula 5 of the preceding paper in a total series of 120 patients with pulmonic stenosis. Table I illustrates that in 36 of 48 consecutive studies selected for presentation in this paper the flow through the pulmonary artery per square meter of body surface was below 3.00 liters per minute which is the normal cardiac index established by Cournand and associates (2). The systemic blood flow, on the other hand, calculated per square meter of body surface according to formula 6 of the preceding paper, showed marked variations above and below the values for normal cardiac index. In 14 patients the rate of flow in the systemic circulation was increased above normal standards. As a result of the increased rate of flow through the peripheral circulation the differences between the oxygen and carbon dioxide contents of peripheral arterial and right auricular bloods were below normal. In 9 individuals the systemic blood flow approximated Cournand's standards for cardiac index, whereas in 13 the systemic flow was below these standards (Table I). In one individual the calculated blood flow through the pulmonary artery was 20 per cent of normal (case # 12, Table I). Although a preoperative diagnosis of pulmonary atresia could not be

* This work was supported by a grant from the Commonwealth Fund.

made for reasons outlined in the preceding paper (1), the extremely low values for pulmonary artery flow suggested the presence of this condition. This assumption was confirmed at operation.

A comparison of the data obtained for systemic flows with those for the pulmonary artery demonstrated that the former exceeded pulmonary artery flow by from 0 to 9.7 liters per minute. This indi-

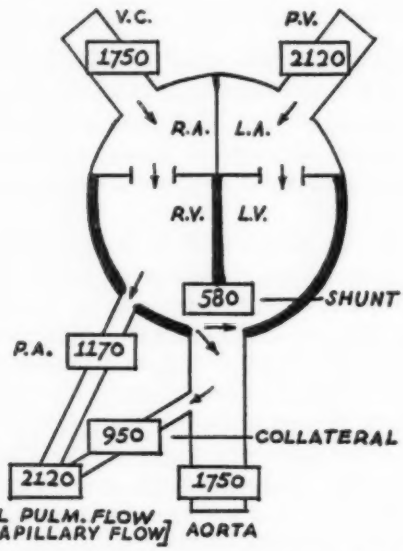

FIG. 1. illustrates the results obtained in a case (E. R. age 17) of tetralogy of Fallot. It may be seen that the systemic flow exceeds that through the pulmonary artery, resulting in a right to left shunt of 580 cc./minute. The pulmonary capillary flow exceeds that through the pulmonary artery, indicating the presence of collateral circulation to the lung of 950 cc./minute.

cated that in tetralogy of Fallot some of the returning mixed venous blood, unable to pass through the stenosed pulmonary artery into the lung, coursed through the interventricular septal defect and the overriding aorta directly into the systemic circulation. Consequently, as illustrated in Fig. 1, which represents a typical case of tetralogy of Fallot, the overall direction of the intracardiac shunt was from right to left. However, there was some concomitant flow from left to right

through the septal defect. This was indicated by the observation that the oxygen content of right ventricular blood exceeded that of the right auricle in the majority of cases (Table I). In 2 individuals (#19 and 34, Table I) both systemic and pulmonary artery flows were reduced below normal values for cardiac index by an equal amount. It could be assumed that in these cases of pulmonic stenosis the accompanying interventricular septal defect was small and the aorta arose chiefly from the left ventricle. This assumption was supported by the fact that the oxygen saturation of peripheral arterial blood in these patients was above 88 per cent despite greatly reduced flow through the pulmonary artery (Table I). These considerations suggested that the variations in systemic flow observed in patients with tetralogy of Fallot were related to the degree of pulmonary stenosis and the size of the intracardiac shunt.

The Pulmonary Capillary Flow (Total Pulmonary Flow): Values for pulmonary capillary flow, calculated according to formula 8 of the preceding paper, are listed in Table II. In most of the younger individuals the values obtained with this method agreed closely with those determined for pulmonary artery flow. In the majority of older patients, however, pulmonary capillary flow exceeded pulmonary artery flow, indicating that the lungs received blood from sources other than the pulmonary artery (Fig. 1). Direct observations of collateral circulation during operation have confirmed these findings (3). A linear relationship, however, between age and the magnitude of collateral circulation has not been obtained. This should be expected since in younger individuals atresia of the pulmonary artery required sufficient collateral circulation for the survival of the individual. A large calculated difference between pulmonary capillary and pulmonary artery flow was found in the oldest person of this series (#6, Table II), who had been clinically classified as a case of Eisenmenger's syndrome. At operation the pleural cavity was found obliterated by adhesions through which innumerable collaterals from intercostal and mammary arteries passed to the lung. In other patients in whom calculations indicated the presence of extensive collateral circulation to the lungs large bronchial and multiple accessory arteries were found. It seemed probable that the collateral circulation to the lung represented an important factor in the physiological adjustments of these individuals to their abnormally low pulmonary artery flow.

TABLE I

Data Obtained by Right Heart Catheterization

NO.	DATE 1946	SUBJ.	AGE	SEX	SURF. AREA M^2	CC. O_2 CONS. *per min.*	CC. CO_2 PROD. *per min.*	CC. CO_2 CALC. *per min.*	R.Q.	MIN. VOL. L/M	B.M.R.	R.V.		P. A.		R. A.		P. V.		P. A.		O_2 CAP. VOL. %	O_2 SAT. %	CARDIAC OUTPUT LITERS/MIN./M^2		RIGHT TO LEFT INTRA-CARD. SHUNT LITER S Min./M^2	NO.
												O_2 Vol. %	CO_2 Vol. %	O_2 Vol. %	CO_2 Vol. %	O_2 Vol. %	CO_2 Vol. %	O_2 Vol. %	CO_2 Vol. %	O_2 Vol. %	CO_2 Vol. %			Pulm.	Syst.		
1	3/12	V. S.	25	M	1.68	241	218		.89	9.7	+9	21.3	35.8			18.8	35.3	32.4		22.5	31.7	34.0	60.6	1.29	3.87	2.57	1
2	3/18	C. H.	15	M	1.6	195	153		.79	6.22	−9	22.	32.4			18.2	36.3	31.3*	25.6*	22.9	33.2	32.5	71.	1.2	2.58	1.38	2
3	3/21	D. M.	10	M	.83	95	85		.87	3.01	−32	18.9	38.1			18.2	41.7	27.3	29.0	22.7	37.3	28.5	79.8	1.37	2.55	1.1	3
4	3/26	D. S.	18	F	1.3	138	117		.83	4.43	−18	18.7	35.6			17.6	37.7	30.4	24.0	20.4	35.7	32.0	63.8	.89	3.7	2.8	4
5	4/17	O. J.	24	M	1.8	162	152		.9	4.5	−30	23.0	44.7			20.4	46.3	30.8	36.0	24.0	43.0	32.0	75.0	1.16	2.52	1.36	5
6	4/23	M. C.	15	F	1.28	161	143		.88	5.25	−5	21.3	37.3			22.8		33.8	29.0	24.3	32.5	35.3	69.0	1.08	8.4	7.5	6
7	4/30	L. S.	26	M	1.68	172	153		.88	5.11	−23	20.2	39.2			22.3	38.2	32.2	32.8	24.4	36.1	34.1	71.5	.85	4.8	4.04	7
8	5/10	J. A. C.	9	F	.98	130	144	110	1.1	7.03	−19	17.2	37.2			14.3	40.8	24.8*	30.8*	17.7	36.4	26.3	67.5	1.05	3.84	2.79	8
9	5/14	T. M.	7	M	.85	132	152	107	1.12	6.84	−15	24.7	31.5			21.9	35.6	31.5	24.9			33.0	65.0	2.03			9
10	5/17	C. H.	21	F	1.43	119	119		1.0	4.5	−34	16.0	40.9			14.6	42.2	25.	30.5	16.0	39.5	26.3	60.8	.93	5.89	4.9	10
11	5/21	R. A.	22	M	1.46	156	157		1.0	6.9	−25	26.7	22.3			23.1	26.4	33.5	22.4	28.9	20.7	35.2	82.0	1.58	1.84	.26	11
12	5/28	G. S.	19	F	1.5	103	113	84	1.08	4.07	−48	19.5	41.8			16.9	45.1	29.9	30.0	24.5	37.6	31.5	77.7	.66	.90	.24	12
13	5/31	R. C.	16	M	1.35	162	207	132	1.26	8.2	−24	18.5	39.3			18.3	40.1	30.4	32.0	22.8	34.9	31.7	72.2	1.01	2.64	1.6	13
14	6/6	A. P.	18	F	1.3	131	109		.82	4.82	−23	11.7	40.3			13.7	40.0	20.0	34.4	18.1	35.8	21.0	85.5	1.18	2.24	1.06	14
15	6/12	L. P.	20	F	1.59	164	134		.81	5.2	−19	19.3	36.0			19.8	35.8	28.8	30.0	24.2	29.4	30.3	79.9	1.08	2.38	1.29	15
16	6/19	J. H.	17	M	1.54	177	147		.82	8.6	−27	22.5	31.2			20.1	34.5	37.7	23.0	22.8	29.8	39.8	57.4	.75	4.2	3.48	16
17	6/26	A. F.	7	M	.66	126	115		.90	6.3	−8	17.3	35.3			17.5	34.3	33.1	24.4	19.9	31.6	34.5	57.8	1.22	8.2	6.9	17
18	7/3	J. O.	18	M	1.68	180	153		.73	4.1	−27	23.8	45.2			22.9	43.6	31.7	38.0	26.6	40.0	33.4	80.0	1.37	2.97	1.6	18
19	7/9	V. H.	5	M	.76	105	91		.83	4.68	−26	12.0	38.3			9.6	37.4	19.0	24.2	17.8	38.8	20.0	89.0	1.98	1.9	0	19
20	7/11	D. F.	12	M	1.34	150	165	122	1.08	6.79	−33	16.9	40.6			16.5	14.4	23.1	35.5	19.4	37.8	24.3	80.1	1.8	3.9	2.0	20
21	7/17	J. F.	8	F	.95	77	72		.90	3.2	−48	17.4	42.9			16.3	41.4	29.8	33.0	20.9	36.1	31.5	66.0	.65	1.75	1.0	21
22	7/23	J. F.	16	M	1.7	211	241	171	1.1	7.9	−23	14.1	40.7	12.8	42.7	12.5	41.8	25.4	33.2	21.0	39.8	26.7	78.6	.9	1.5	.5	22
23	7/26	E. R.	17	F	1.43	112	122	91	1.08	4.9	−39	17.8	38.5			18.1	38.2	27.6	36.5	24.6	39.5	29.1	84.5	.8	1.23	.4	23

24	8/6	B. H.	8	F	.96	111	132	90	1.18	7.17	−28	14.3	42.0			14.8	42.5	22.2	32.3	17.1	37.6	23.3	73.4	1.47	5.16	3.67	24
25	9/4	D. B.	7	M	.77	95	97	77	1.02	5.8	−24	14.2	34.3			12.1	34.5	28.8	18.7	17.9	29.7	30.4	58.6	.8	2.1	1.2	25
26	9/5	V. B.	14	F	1.01	123	107		.87	6.28	−24	16.7	39.7	16.3	38.5	15.2	40.2	26.7	29.1	21.1	35.0	28.2	75.0	1.17	1.25	.87	26
27	9/11	C. P.	11	M	1.21	132	117		.89	7.02	−31	18.9	36.7	21.1	35.8	20.2	35.1	31.1	27.7			32.7	55.0	1.09			27
28	9/18	R. W.	18	M	1.5	195	231	159	1.18	11.8	−15	24.8	35.0			20.5	39.6	31.4	29.6	26.8	31.	33.0	81.0	1.97	2.06	.08	28
29	9/21	R. F.	10	F	1.02	161	142		.88	8.0	−1	26.8	36.5	24.8	38.2	19.3	14.9	32.5	28.9	24.2	39.4	34.0	70.9	2.06	3.24	1.18	29
30	10/4	J. McM.	10	M	1.14	153	166	124	1.09	7.95	−4	13.8	39.4			12.8	41.4	22.2	34.5	14.4	40.9	24.5	58.5	1.61	8.5	6.78	30
31	10/15	J. M.	5	F	.82	91	90		.98	4.15	−38	16.9	41.0	16.7	40.2	18.3	44.7	23.4	32.8	19.3	41.7	24.7	78.0	1.64	11.4	9.7	31
32	10/21	A. S.	21	F	1.59	148	131		.89	6.2	−26	14.25	41.7			13.7	40.2	22.9	36.8	18.0	35.4	24.1	74.8	1.07	2.18	1.11	32
33	10/29	A. O. C.	12	M	.93	96	80		.83	4.15	−41	17.3	38.7			17.0	38.0	29.1	24.6	19.6	35.0	30.4	64.5	.92	3.3	2.39	33
34	11/8	S. C.	14	M	1.5	135	140	109	1.03	6.9	−46	18.7	38.2	18.8	37.	17.1	39.8	24.4	31.2	23.1	34.0	25.5	91.0	1.6	1.5		34
35	11/11	A. deH.	9	F	.9	102	125	83	1.23	4.82	−30	20.2	41.5			18.3	44.9	26.6	35.2			28.0	61.8	1.48			35
36	11/14	E. L.	20	F	1.44	215	220	172	1.01	7.35	+18	19.5	38.8			19.1	38.2	26.3	30.2	22.6	35.0	27.7	82.5	2.2	4.2	2.06	36

* Direct determination

Of further interest were 4 cases in which the clinical findings indicated the presence of a patent ductus arteriosus together with reduced pulmonary artery flow (#4, 9, 19, 20, Table II). Figure 2, which presents the findings in one of these cases, demonstrates that the pulmonary capillary flow exceeded the flow through the pulmonary artery, because of a large collateral circulation to the lung contributed by the

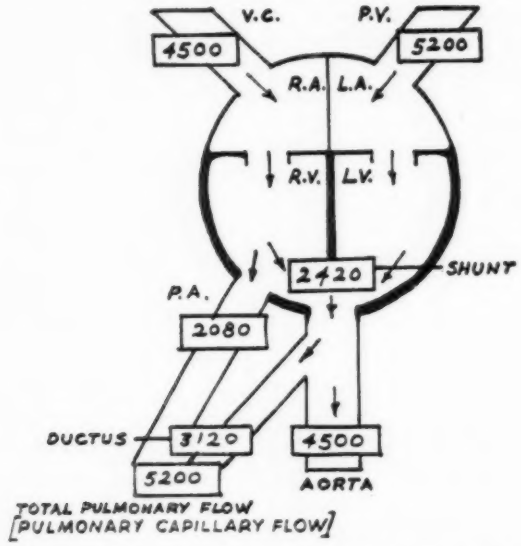

FIG. 2. represents the volume flows in a patient O. J. age 24 with tetralogy of Fallot and patent ductus arteriosus. The intracardiac right to left shunt is 2420 cc./minute. The volume flow in the ductus, calculated as the difference between pulmonary capillary and pulmonary artery flows, is 3120 cc./minute.

ductus. Confirmatory evidence for the existence of a patent ductus arteriosus in the presence of pulmonary stenosis has not been obtained in these individuals since operation has not been performed. However, the combination of clinical and physiological data strongly suggested the combination of a patent ductus and pulmonary stenosis.

Blood Pressures and Peripheral Resistance: Intracardiac and systemic blood pressures were obtained in a series of 22 patients with clinical

and physiological evidence of tetralogy of Fallot. Table III shows that the right intraventricular systolic pressure was elevated in every instance except one (# 21, Table III); pressures recorded ranged from 20 to 110 mm. above the normal values of 18 to 28 mm. of mercury. The diastolic pressure in the right ventricle was elevated in 8 cases (Table III). It is probable that in several individuals the high diastolic pressures were the result of backward failure which was clinically manifest in these individuals. In 6 cases where the catheter was passed into the pulmonary artery through the stenosis, a sharp fall in pressure was observed (Fig. 3). In some of these individuals the pulmonary artery pressures were so low that only the slightest excursions are recorded. It seemed of special interest that in a large number of cases systolic pressures in the femoral artery were of the same order as those in the right ventricle (Table III), although the pressures were not recorded simultaneously. Complete agreement in the heights of the systolic pressures existing in the right ventricle and the aorta was obtained in 3 subjects in whom the catheter was passed from the right ventricle through the aortic valve (Fig. 4) indicating equilibration of pressures in the two chambers.

In 19 cases the peripheral resistance was calculated according to the formula of Aperia, which mathematically expresses the ratio between pressure and resistance (4). Table III shows that values obtained for peripheral resistance ranged from 600 to 6000 dynes/sec/cm^5/M^2., while the blood pressures remained approximately constant. Consequently a logarithmic relationship existed between systemic flow and peripheral resistance (Fig. 5). Since the results reported in the preceding paragraphs indicated that the variations in systemic flow were related to the size of the intracardiac shunt, it would appear that changes in the peripheral resistance occurred as a compensatory response to the alterations in flow.

Oxygen Consumption and Basal Metabolic Rate: Table I demonstrates that the oxygen consumption in the great majority of individuals with decreased effective pulmonary flow was reduced. A similar observation has been made by Dexter (5). The basal metabolic rate calculated from these figures ranged as low as −48. This finding was of considerable interest since it suggested that the decrease in the overall metabolic processes might be the result of prolonged anoxemia.

TABLE II

Data Obtained by the Equilibration Method for the Determination of Pulmonary Capillary Flow

NO.	DATE 1946	SUBJ.	SEX	AGE	SURF. AREA M^2	CC. CO_2 PROD. *per min.*	CC. CO_2 CALC. *per min.*	R.Q.	M.V.L/M	CO_2 INCOMING CAP. BLOOD			CO_2 OUTGOING BLOOD			LITERS TOTAL PULM. FLOW/M^2	CC. COLLAT. FULM. FLOW/M^2	NO.
										%	Tension mm. Hg.	Vol. %	%	Tension mm. Hg.	Vol. %			
1	3/13	C. H.	M	15	1.6	215	147	1.18	7.64	5.14	36.4	31.0	3.18	22.5	23.0	1.1	0	1
2	3/18	D. M.	M	10	.83	123		1.0	4.17	5.35	38.2	37.5	3.09	22.0	26.6	1.3	0	2
3	3/27	D. S.	F	18	1.32	117		.83	4.45	4.40	31.5	31.0	3.50	25.0	25.0	1.5	574	3
4	4/16	O. J.	M	24	1.78	172		.96	4.5	4.8	34.7	39.1	4.17	29.8	35.8	2.9	1752	4
5	4/22	M. C.	F	15	1.28	162.5		.93	6.44	4.38	31.3	33.0	2.76	19.8	25.7	1.7	720	5
6	4/29	L. S.	M	26	1.25	237	162	1.18	5.88	4.86	34.8	38.8	3.75	26.9	32.6	2.0	1132	6
7	5/8	J. A. C.	F	9½	.98	108.7		.93	4.81	4.98	35.3	35.3	2.68	19.0	24.5	1.0	0	7
8	5/13	T. M.	M	7½	.85	137.7	93.9	1.18	6.33	4.17	29.8	31.5	2.76	19.0	24.9	1.7	0	8
9	5/16	C. H.	F	21	1.43	118		.96	4.8	4.48	31.9	36.8	3.52	25.3	32.8	2.5	1518	9
10	5/22	R. A.	M	22	1.46	157.5		1.62	6.93	3.94	28.0	27.2	2.8	20.1	22.4	2.2	643	10
11	5/24	A. P.	F	18	1.3	113.2		.93	5.01	4.69	33.75	38.8	3.80	27.3	35.0	2.3	1065	11
12	5/29	G. S.	F	19	1.5	144	99.6	1.15	5.0	4.97	35.5	37.3	3.5	25.4	31.0	1.2	515	12
13	6/3	R. C.	M	16	1.35	206	131.7	1.26	8.2	4.5	32.0	36.2	3.35	23.8	31.5	2.1	1060	13
14	6/5	S. E.	M	19	1.7	159	119	1.07	6.75	4.95	35.3	41.7	4.07	24.1	38.2	2.0	0	14
15	6/11	L. P.	F	20	1.59	134		.81	5.2	4.51	32.4	34.4	3.39	24.2	28.8	1.5	423	15
16	6/12	V. H.	M	5	.76	90.8		.83	4.7	3.76	26.8	29.8	2.62	18.68	24.2	2.2	170	16
17	6/19	J. H.	M	17	1.54	147		.82	8.6	4.2	30.3	29.2	2.9	20.6	24.0	1.8	1083	17
18	6/29	J. O.	M	18	1.68	153		.86	4.7	5.1	36.5	41.1	4.3	31.2	38.0	2.9	1575	18
19	7/10	D. F.	M	12	1.34	179.6	117.8	1.2	6.6	4.3	30.0	37.2	3.8	27.1	35.1	4.2	2361	19
20	7/16	J. F.	F	8	.99	73.1		.9	3.5	3.9	28.0	35.2	3.2	23.6	32.6	3.0	2310	20
21	7/22	J. F.	M	16	1.70	241	171	1.1	7.9	4.8	34.2	36.8	4.4	31.3	34.2	3.8	2790	21
22	7/29	E. R.	F	17	1.43	121	91	1.08	4.9	5.03	36.0	40.8	4.1	29.4	36.6	1.5	660	22
23	8/5	B. H.	F	8	.96	98	69	1.15	5.9	4.8	34.3	39.7	3.4	24.0	32.0	9.4		23
24	9/4	V. B.	F	14	1.01	88.3		.71	4.5	4.5	32.7	34.5	3.4	24.8	29.1	1.6	445	24

25	9/7	D. B.	M	7	.77	97	76	1.02	5.8	3.9	28.0	26.0	2.3	16.7	18.7	1.4	524	25
26	9/10	C. P.	M	11	1.21	93		.91	6.4	4.05	28.9	31.0	3.4	24.1	27.7	2.4	1260	26
27	9/12	W. B.	M	15	.91	77.8		.88	5.5	3.26	23.4	27.8	2.19	15.7	23.2	1.9		27
28	9/13	A. S.	M	25	1.62	193.5	146.5	1.06	6.84	4.9	36.0	40.0	4.5	32.2	37.0	3.0	990	28
29	9/17	R. W.	M	18	1.5	231	156	1.18	11.8	4.03	29.0	32.0	3.39	24.4	29.6	2.98	1480	29
30	9/20	R. F.	F	10	1.2	108		.96	5.21	4.14	29.5	31.3	3.5	24.6	28.3	3.5	1480	30
31	9/23	F. C.	F	14	1.22	138	97	1.5	8.9	3.25	23.2	26.2	2.6	19.8	23.5	2.9		31
32	10/1	J. M.	M	10	1.14	166	123.5	1.09	7.95	4.78	34.1	38.0	3.84	27.4	34.5	2.3	710	32
33	10/12	J. M.	F	5	.82	89.7		.98	4.15	4.59	32.7	37.6	3.64	25.7	32.8	2.3	610	33
34	10/18	A. S.	F	21	1.59	171.5	132	1.07	7.55	5.15	36.2	41.0	3.69	25.9	36.2	1.8	685	34
35	10/28	A. O.	M	12	.93	80		.83	4.15	4.81	34.7	33.8	3.23	23.5	26.6	1.0	150	35
36	11/7	A. D.	F	9	.90	92.0	72.5	1.03	4.97	4.75	33.8	37.4	4.13	29.5	35.2	3.70	1200	36
37	11/7	S. C.	M	14	1.5	198	128.5	1.24	10.6	4.46	31.8	33.9	3.88	27.2	31.2	3.20	1560	37
38	11/13	E. L.	F	20	1.44	127		.92	4.41	4.55	32.5	35.5	3.81	27.2	32.3	3.7	1540	38

Although a similar trend was obtained by Lilienthal and Riley in men during anoxia of short duration (6) and by Ogata in rabbits (7), most observers did not notice a reduction in the oxygen consumption of

TABLE III

Intraventricular and Peripheral Blood Pressures and Calculated Peripheral Resistances

NO.	DATE 1946	SUBJECT	SEX	AGE	PRESSURE FEMORAL ARTERY MM. HG.			PRESSURE RIGHT VENTRICLE MM. HG.		SYSTEM. FLOW LITERS/ MIN./M²	PERIPHERAL RESISTANCE DYNES. SEC./CM⁵/M²	NO.
					Syst.	Diast.	Mean	Syst.	Diast.			
1	8/5	B. H.	F	8	120	75	105	128	0	5.16	1630	1
2	9/3	V. B.	F	13	139	86	98	115	9	1.25	6250	2
3	9/9	D. B.	M	10	92	60	70	111	0	2.10	2660	3
4	9/11	C. P.	M	11	94	60	79	128	16	4.5	1404	4
5	9/16	A. S.	M	24				140	0			5
6	9/20	R. F.	F	10	165	100	118	84	14	3.24	2910	6
7	9/23	J. V.	M	12	115	98	106		0			7
8	9/25	R. W.	M	19	120	94	104		0	2.06	4035	8
9	10/4	J. McM.	M	10	128	70	90	58	19	8.5	846	9
10	10/7	B. A.	F	8	92	80	87		0			10
11	10/11	E. R.*	F	17	145	82	96	65 to 100	0	2.14	3740	11
12	10/14	G. W.	M	26	143	90	106		0	2.58	3300	12
13	10/15	J. M.	F	5½	150	88	98	107	6	11.4	685	13
14	10/21	A. S.	F	21	105	71	82	124	6	2.18	3020	14
15	10/29	A. OC.	M	12	121	92	106	116	15	3.3	2570	15
16	11/8	S. C.	M	14	138	83	100	94	0	1.5	5320	16
17	11/11	A. deH.	F	9	126	69	88	96	0	5.95	1185	17
18	11/14	E. L.	F	20	141	96	111	125	20	4.3	2084	18
19	11/22	B. P.	F	11	148	94	116	132	0	11.4	813	19
20	11/25	R. G.	M	8	92	73	82	109	0	8.5	775	20
21	12/3	A. C.	M	15	112	84	93	20	0	3.1	2380	21
22	12/5	G. T.	M	12	114	95	104	143	23	2.9	2850	22

* Postoperative observation.

individuals or animals after prolonged exposure to low barometric pressure (8). It is conceivable that the difference in the results reported was due to the fact that the anoxia produced under experimental conditions was of considerably shorter duration (6, 7). It also seemed probable that the poor nutritional status observed in many of these patients was at least partially responsible for the decreased oxygen

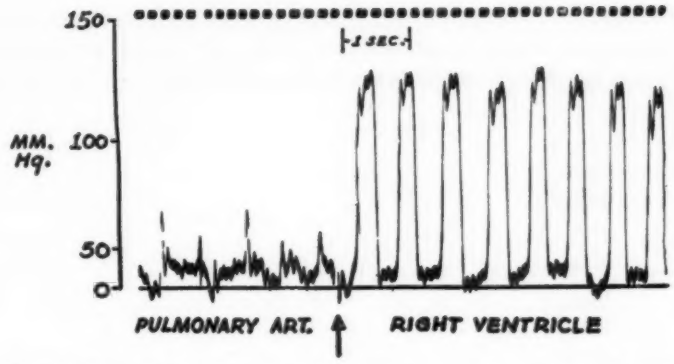

FIG. 3. shows the continuous optical pressure recordings obtained from the pulmonary artery and the right ventricle of a patient G. T. age 12 with tetralogy of Fallot. As the catheter tip was withdrawn from the pulmonary artery into the right ventricle through the semilunar valve (arrow in figure), the systolic pressure rose from 69 to 143 mm. mercury. This demonstrates the presence of pulmonic stenosis. The elevation of the intracardiac diastolic pressure indicates right ventricular strain.

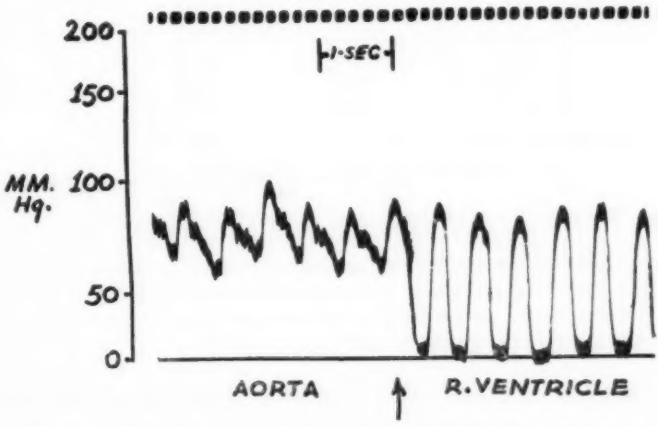

FIG. 4. shows continuous optical recordings obtained from the aorta and the right ventricle of a patient L. P. age 5 with tetralogy of Fallot. Withdrawal of the catheter tip through the aortic valve (arrow in figure) results in a sharp fall of the diastolic pressure, with the systolic pressure remaining constant.

consumption. Findings which will be reported in a subsequent paper demonstrated that the basal metabolic rate of individuals with reduced effective pulmonary blood flow increased considerably following per-

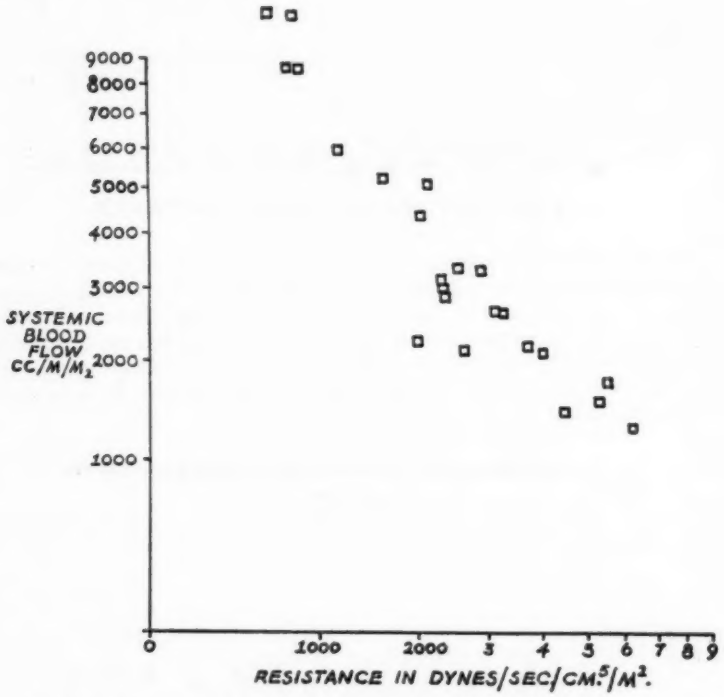

FIG. 5. illustrates the relationship between peripheral resistance and systemic blood flow plotted logarithmically in 23 cases of tetralogy of Fallot. Since the mean pressures remain constant, the variations in systemic flow are responsible for the alterations in the peripheral resistance.

formance of the Blalock-Taussig operation, which raises pulmonary flow.

Results of the Exercise Test: A standard exercise test as described in the preceding paper was performed in a series of 21 patients. As seen in Table IV, in 14 out of 21 cases the ratio of oxygen consumed

per liters of ventilation during exercise fell below its resting value and the carbon dioxide produced per liters of ventilation also declined in 16 individuals. Figure 6 illustrates these results in a typical case of

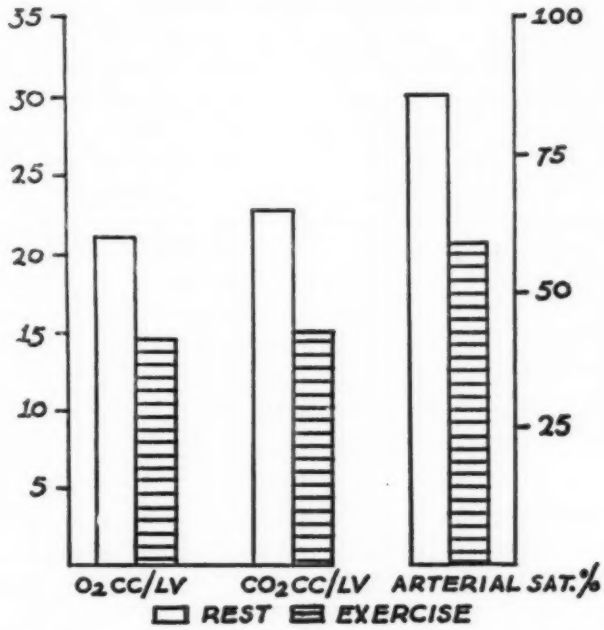

FIG. 6. demonstrates the results of a standard exercise test obtained in a patient E. R. age 17 with tetralogy of Fallot. It can be seen, that in contrast to results obtained in normal individuals, the oxygen consumed and the carbon dioxide produced per liter of ventilation as well as the arterial oxygen saturation declined.

tetralogy of Fallot. This was contrary to observations on normal individuals in whom the standard exercise results in a significant increase in the oxygen and a slight rise in the carbon dioxide ratios (9). This fall in the ratios in individuals with pulmonic stenosis was apparently the result of limited circulating volume of mixed venous blood through the lung during exercise. In contrast to these findings were the results obtained in some individuals who had developed large collateral circu-

lation to the lung. In one of these cases (#2, Table IV) the collateral flow was 1480 cc./M². Data in Table IV demonstrate that in

TABLE IV

Results Obtained with the Standard Exercise Test

NO.	DATE 1946	SUBJ.	AGE	SEX	VENT. LIT./MIN./M²	CO_2 CC. M²	CO_2 CC. LV	O_2 CC. M²	O_2 CC. LV	R.Q.	ART. O_2 VOL%	ART. CO_2 VOL%	ART. CAP. VOL%	ART. SAT. %	NO.
1	6/17	J. H.	17	M	Rest 5.88	107.0	18.2	154.0	17.0	1.07	25.1	25.1	39.8	63.4	1
					Ex. 12.4	185.0	14.8	268.0	14.9	1.07	18.4		39.8	46.1	
2	6/21	C. B.	17	M	Rest 6.15	122.0	19.7	96.5	15.7	1.26	17.6	36.2	25.2	70.0	2
					Ex. 8.28	175.0	21.5	132.0	15.9	1.34	14.5	36.9	25.2	57.0	
3	6/25	C. G.	9	F	Rest 7.30	129.0	17.6	92.4	12.7	1.38	16.5	29.9	34.2	48.4	3
					Ex. 16.5	218.0	13.3	147.0	8.9	1.47	13.2	31.5	34.2	38.8	
4	7/1	J. O.	18	M	Rest 4.77	91.4	32.0	105.0	36.8	0.86	25.8	41.1	33.3	77.4	4
					Ex. 7.51	138.0	30.8	148.0	33.1	0.92	20.0	44.8	33.3	60.4	
5	7/8	V. H.	5	M	Rest 6.18	120.0	19.4	139.0	22.5	0.83			20.0	89.0	5
					Ex. 16.12	295.0	18.1	276.0	17.0	1.06			20.0	48.0	
6	7/10	D. F.	12	M	Rest 4.96	134.0	26.9	109.0	21.8	1.23	19.4	41.3	24.3	80.0	6
					Ex. 7.46	184.0	24.7	253.0	33.9	0.72	12.2	45.2	24.3	50.1	
7	7/16	J. F.	8	F	Rest 3.69	77.0	20.8	76.4	20.7	0.99	21.1	35.1	31.5	66.0	7
					Ex. 12.45	195.8	15.7	158.0	12.6	1.24	12.0	41.4	31.5	31.2	
8	7/22	J. F.	16	M	Rest 4.68	141.7	30.2	122.7	26.5	1.12	21.0	39.8	26.7	78.6	8
					Ex. 8.29	198.9	24.0	166.4	20.3	1.15	14.4	42.3	26.7	54.1	
9	7/24	E. R.	17	F	Rest 4.47	104.6	23.4	95.4	21.3	1.14	24.6	32.5	29.0	84.7	9
					Ex. 11.33	178.2	15.7	165.2	14.6	1.08	17.1	34.8	29.0	59.1	
10	8/5	B. H.	8	F	Rest 6.18	102.0	16.5	88.2	14.3	1.15	17.1	37.6	23.3	73.4	10
					Ex. 11.25	194.0	18.0	164.0	15.3	1.18	14.3	45.3	23.3	18.7	
11	9/6	V. B.	14	F	Rest 4.42	87.4	19.7	121.0	27.6	0.71	21.1	35.0	28.2	75.3	11
					Ex. 17.1	198.0	11.6	106.0	6.2	1.87	10.4	38.0	28.2	36.9	
12	9/16	R. W.	18	M	Rest 7.68	150.0	19.5	102.5	16.4	1.18	26.8	31.0	33.0	81.0	12
					Ex. 11.32	238.0	20.7	215.0	19.0	1.09	20.4	34.9	33.0	61.8	
13	9/21	R. F.	10	F	Rest 5.1	106.0	20.8	122.0	23.9	0.96	24.2	39.4	34.2	70.9	13
					Ex. 8.96	182.0	20.4	182.0	20.4	1.0	22.8	37.8	34.2	67.0	
14	9/24	F. C.	14	F	Rest 7.3	114.0	15.5	99.0	13.5	1.5	18.4	30.3	26.6	69.1	14
					Ex. 11.1	167.0	14.8	153.5	13.7	1.1	17.1	30.4			
15	10/2	J. M.	10	M	Rest 6.97	145.6	20.9	133.5	19.1	1.09	14.3	40.9	24.5	58.5	15
					Ex. 15.6	198.1	12.7	140.2	8.9	1.42	8.3	35.2	24.5	33.8	
16	10/22	A. S.	21	F	Rest 3.9	82.5	21.1	93.0	23.9	0.89	18.0	35.4	24.1	74.8	16
					Ex. 11.9	228.0	20.9	183.0	16.8	1.24	12.0	36.6	24.1	50.0	
17	10/30	A. O.	12	M	Rest 4.3	82.0	19.0	99.0	23.0	0.83	19.6	36.1	30.4	64.5	17
					Ex. 13.2	210.0	15.8	244.0	18.4	0.85	14.3	33.8	30.4	47.0	
18	11/9	S. C.	14	M	Rest 4.6	93.5	20.3	90.0	19.5	1.00	23.1	34.0	25.5	91.0	18
					Ex. 9.9	210.0	21.1	222.0	22.5	0.93	19.1	36.1	25.5	74.5	
19	11/13	A. H.	9	F	Rest 5.07	139.0	26.0	113.5	22.3	1.2	17.3	40.6	28.0	61.8	19
					Ex. 13.2	249.5	18.9	214.5	16.3	1.16	15.4	41.6	28.5	54.2	
20	11/15	E. L.	20	F	Rest 5.32	130.0	24.4	157.0	29.7	0.80	22.8	35.0	27.7	82.5	20
					Ex. 7.78	175.0	22.5	248.0	32.0	1.72	11.7	36.1	27.7	42.5	
21	12/3	A. C.	15	M	Rest 5.27	95.5	18.1	89.5	16.9	1.06	17.9	30.8	33.4	44.0	21
					Ex. 11.55	147.5	12.7	156.5	13.5	0.95					

this individual the ratio of oxygen consumed per liters of ventilation rose from 16.4 to 19.0. This indicated that the collateral circulation

combined with the flow through the pulmonary artery was adequate to cope with the increased respiratory demands of exercise. Table IV demonstrates that in 14 of 21 patients the respiratory quotient rose during exercise. This is in contrast to the observations of Cournand and Richards (9) who found a slight fall in normal individuals. An explanation for this observation is not possible at present.

In every instance the measurement of the breathing requirements described above was accompanied by a comparison of the oxygen and carbon dioxide contents obtained from arterial blood drawn preceding and following the standard exercise. In contrast to normal individuals (9), the patients studied in this series showed a marked decline in arterial oxygen saturation, and a rise in carbon dioxide content following the exercise (Table IV and Fig. 6). Similar results were observed in patients with large collateral circulation, in cases belonging to Eisenmenger's syndrome, and in some of the patients after the performance of the Blalock-Taussig operation (10). This demonstrated that the fall in arterial oxygen saturation after exercise observed in patients with normal rate of flow through the lung must have been caused by increased shunting of venous blood into the systemic circulation.

DISCUSSION

The results of the tests described in the preceding paragraphs demonstrate a reduction in pulmonary artery flow of from 1000 to 2000 cc. below normal cardiac index, depending on the degree of the stenosis. In one patient (# 12, Table I) in whom the calculated rate of flow through the pulmonary artery is only 20 per cent of normal, atresia of that vessel was found at operation. The systemic flow, calculated per square meter of body surface, shows marked variations above and below values for normal cardiac index (Table I). In normal individuals, variations in the overall circulating volume of blood flow are usually the result of functional changes. With varying degrees of pulmonic stenosis and interventricular septal defect, however, the systemic blood flow depends to a large extent on the volume of the intracardiac shunt (Fig. 1). Table I illustrates that in most cases of tetralogy of Fallot the systemic flow exceeds that through the pulmonary artery, indicating that the overall direction of the intracardiac shunt is from right to left. Consequently the systemic blood flow will be partic-

ularly high in individuals with severe pulmonic stenosis, large interventricular septal defects, and marked overriding of the aorta. In patients with a moderate degree of pulmonic stenosis and small septal defects, where the aorta arises chiefly from the left ventricle, the systemic flow will approach normal. It will be decreased in cases of uncomplicated pulmonic stenosis where both systemic and pulmonary artery flows must be reduced below normal by an equal amount. It is apparent, therefore, that the hemodynamics of the systemic flow in tetralogy of Fallot depend to a large extent on mechanical factors brought about by the cardiac malformation.

The results obtained from an application of the indirect Fick principle to the determination of pulmonary capillary flow indicate that in some cases of tetralogy, as in normal individuals (10), the values obtained with this method agree closely with those determined for pulmonary artery flow. This demonstrates the absence of measurable collateral circulation to the lung in these individuals. In the majority of patients with pulmonic stenosis, however, pulmonary capillary flow exceeds pulmonary artery flow, indicating that the lung receives a considerable flow of blood from sources other than the pulmonary artery (Fig. 1). Collateral circulation in these individuals represents an important physiological mechanism in offsetting the effect of pulmonic stenosis by increasing the flow of mixed venous blood through the lung. The anatomical character of these collaterals is of considerable interest. Large bronchial arteries are commonly observed in these patients. In one case (#6, Table II) which shows a large calculated difference between pulmonary capillary and pulmonary artery flow, innumerable collaterals were seen to pass from intercostal and mammary arteries to the lung at operation. It is significant that in several individuals extensive collateral circulation has been responsible for the erroneous clinical diagnosis of Eisenmenger's syndrome. On fluoroscopy expansile pulsations which are characteristic in Eisenmenger's syndrome are also frequently observed in individuals with large collateral circulation.

The value of combining the determination of pulmonary artery with pulmonary capillary flow is demonstrated further in 4 patients (#4, 9, 19, 20, Table II), in whom clinical evidence suggests the presence of a patent ductus in addition to pulmonary stenosis. In

these individuals the volume of flow through the ductus is represented by the difference between pulmonary capillary and pulmonary artery flow (Fig. 2). An estimation of the rate of blood flow through the patent ductus is of considerable importance as surgical construction of an additional ductus by the Blalock-Taussig operation might be indicated if the natural anastomosis is too small.

Intraventricular pressure curves obtained in pulmonary stenosis reveal the systolic pressure in the right ventricle to be 20 to 110 mm. Hg above normal values. In most instances the pressure rises sharply and falls rapidly during the ejection phase (Fig. 3). A large series of recordings show characteristic features of right ventricular failure. This is demonstrated by the observation that in 8 out of a total of 22 recordings the general level of the ventricular diastolic pressure is elevated above the minimum values which occur early in diastole.

In cases where the catheter is passed into the pulmonary artery through the stenosis, a sharp fall in pressure is observed (Fig. 3). In 3 subjects in whom the catheter was passed from the right ventricle into the overriding aorta, complete agreement in the height of the two systolic pressures was obtained (Fig. 4). Since the oxygen contents of right ventricular blood fall within range of those in the femoral artery in some cases (Table I), it can be assumed that in these instances extensive interventricular admixture of blood leads to equilibration of pressures and gas blood concentrations of the two chambers. This conclusion is similar to that reached by Richards in his patient with tetralogy of Fallot (11).

The results summarized in Table III illustrate that the peripheral resistance varies from 600 to 6000 dynes/sec/cm^5/M^2. The mean systemic pressure, on the other hand, shows only small variations from the normal. According to Aperia's mathematical expression of Poiseuille's law (4), the blood flow must vary inversely with the resistance if the pressure remains constant. Figure 5 illustrates this relationship in the patients studied. As the systemic flow increases, the peripheral resistance declines logarithmically. The importance of mechanical factors in determining the volume flow through the systemic circulation has been discussed in one of the preceding paragraphs; therefore, the variations in peripheral resistance may be considered as circulatory adjustments to changes in volume flow.

The decrease of the oxygen consumption in individuals with tetralogy of Fallot is of considerable interest since it might represent a physiological adaptation to chronic anoxia. The anoxemia observed in these patients may be compared to that present in anoxemia of high altitude. It is believed at the present moment that the oxygen consumption is independent of variations in barometric pressure (8). Only Ogata (7) reports a decrease of the oxygen consumption of rabbits exposed to severe anoxia, and Lilienthal and Riley (6) describe a slight fall in the oxygen consumption of men subjected to low oxygen tensions for short periods of time. Most observations of respiratory metabolism in anoxia in man extend of necessity for periods of several hours or days only. In individuals with cyanotic heart disease, however, the anoxia, usually present from birth, is of much longer duration. It is conceivable, therefore, that the time factor may play a rôle in the decrease of the basal metabolic rate during anoxia. Another possible explanation for the reduction of the basal metabolism in individuals with the cyanotic type of congenital heart disease may be found in the generally poor nutritional status of these patients. A great many are underweight and in some of them the restriction of physical activity is accompanied by a low caloric intake. It has been shown by a number of workers that chronic undernutrition can produce a reduction in the basal metabolic rate (12). It is impossible at present to ascertain which factors are responsible for the decrease in respiratory metabolism. Studies are under way to elucidate this problem.

Table IV shows that in 14 of 21 cases the ratio of oxygen consumed per liters of ventilation falls during the standard exercise test of Cournand and Richards (9). The ratio of carbon dioxide produced per liters of ventilation also declines during exercise in 16 patients (Table IV and Fig. 6). It is probable that the fall in these ratios is the result of the pulmonic stenosis which limits the effective pulmonary blood flow during exercise. As a result, the oxygen consumption and carbon dioxide production cannot rise in proportion to the increase in the minute volume of respiration. In patients in whom the ratio of oxygen consumed per liters of ventilation remains constant or rises, pulmonary artery flow is either normal, or large collateral circulation supplies enough mixed venous blood to take care of the increased respiratory demands of exercise.

The arterial oxygen saturation decreases in every instance immediately following the standard exercise (Table IV and Fig. 6). Simultaneously the arterial carbon dioxide content increases. Inadequate effective pulmonary blood flow which causes the decline in the ratios of oxygen consumed and carbon dioxide produced per liters of ventilation, cannot be responsible for the changes in arterial blood

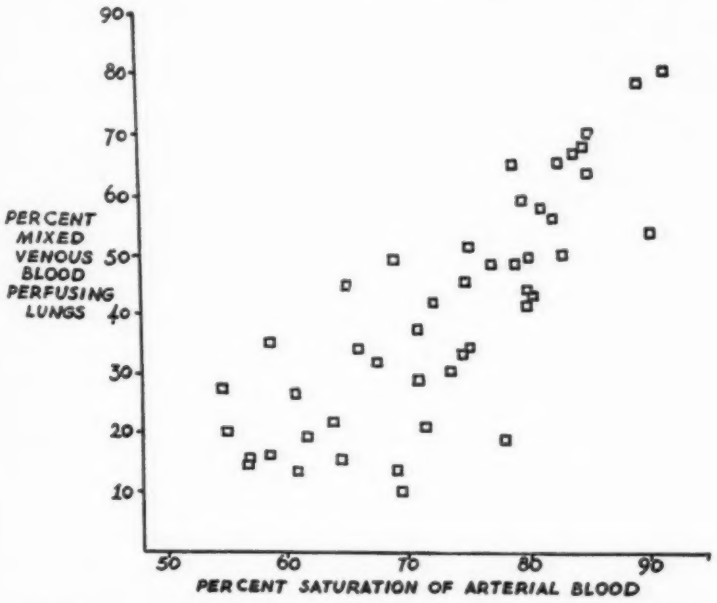

FIG. 7. represents the effect of changes in the percentage of total mixed venous blood perfusing the lung on the arterial oxygen saturation of 46 patients with tetralogy of Fallot. As the percentage of the total mixed venous flow which reaches the pulmonary epithelium increases, the arterial oxygen saturation also rises.

gases. Even in severely anoxemic patients the blood reaching the left auricle is fully saturated with oxygen (1). It is therefore probable that shunts through the interventricular septal defect and the overriding aorta are responsible for the fall in oxygen saturation and the rise in carbon dioxide content of arterial blood during exercise. Additional evidence for this assumption is furnished by observations in patients

with Eisenmenger's syndrome and in some postoperative cases of tetralogy of Fallot, where the pulmonary flow is normal. Here too the standard exercise results in a fall in arterial oxygen saturation. Moreover, adequate pulmonary capillary flow is indicated by a rise in the ratio of oxygen consumed and carbon dioxide produced per liters of ventilation. In cases of interventricular septal defect, admixture of unsaturated with fully oxygenated blood is responsible for a fall in the arterial oxygen saturation. Therefore, a comparison of the gas exchange and minute volume with the arterial oxygen saturation at rest and during exercise is of great value in the recognition of the nature of the cardiac defect.

The preceding discussion has stressed the interrelationship of venous-arterial shunts and decreased pulmonary blood flow in the production of anoxemia. Further considerations indicate that the basic action of both factors is through their effect on volume of mixed venous flow through the lung (the effective pulmonary blood flow). This, as defined in the preceding communication (1), represents the volume of systemic blood which, after passing through the right auricle, reaches the alveolar capillaries. It is seen in Figure 7 that the arterial oxygen saturation is a direct function of the percentage of the total mixed venous blood which passes through the lung. On the basis of this relationship, a decrease in pulmonary capillary flow existing in conjunction with intracardiac shunts contributes to arterial oxygen saturation only by reducing the effective pulmonary blood flow. A large right to left shunt will cause anoxemia for the same reason. In uncomplicated pulmonic stenosis reduction in pulmonary flow alone, however, does not produce arterial oxygen unsaturation, since in such a case all the mixed venous blood reaches the alveolar capillaries.

SUMMARY

120 patients with tetralogy of Fallot have been studied. The results of physiological studies in 48 consecutive cases have been presented.

The blood flow through the pulmonary artery was found to be reduced in relation to the degree of stenosis. The systemic flow ranged above and below values for normal cardiac index. The variations in the systemic flow were related to the size of the intracardiac shunt, which was directed from right to left.

In most cases pulmonary capillary flow exceeded pulmonary artery flow, demonstrating the presence of collateral circulation to the lung.

The systolic pressure in the right ventricle was elevated and approximated the systolic pressure in the systemic circulation. In some instances diastolic pressures were also above normal. As the systemic mean blood pressure was within normal range, the peripheral resistance varied logarithmically with the systemic flow.

The basal metabolic rate was below normal. The possible reasons for this finding were discussed.

During the standard exercise test the ratios of oxygen consumed and of carbon dioxide produced per liters of ventilation decreased, while the arterial oxygen saturation dropped immediately following the exercise. The diagnostic significance of this test was discussed.

The importance of the effective pulmonary blood flow in the production of anoxemia was emphasized.

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THE LIPOTROPIC EFFECT OF N^1-METHYLNICOTINAMIDE[1]

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It has been shown that the F_2 product of nicotinamide metabolism (1, 2, 3) is a methylated compound, namely N^1-methylnicotinamide (4, 5, 6). Since this compound is a normal constituent of body tissue and body fluids, it became desirable to ascertain whether this methylation reaction that takes place in the liver (7, 8) is a reversible one.

In an earlier report Najjar and Deal (9) showed that when 2% N^1-methylnicotinamide chloride was fed to a small group of rats, incorporated in a diet containing glycocyamine, the amount of fat deposited in the livers of those rats was appreciably lower than that obtained in the control animals not receiving the methyl compound. Handler and Dubin (10), using a different diet supplemented with 1% N^1-methylnicotinamide alone or with homocystine, did not obtain any lipotropic activity. To test this effect further additional experiments were performed using a larger group of rats.

EXPERIMENTAL

Three types of experiments were performed. They were designed to show 1) the effect of N^1-methylnicotinamide alone on liver lipids, 2) the effect of N^1-methylnicotinamide in conjunction with glycocyamine as a methyl acceptor and 3) to investigate the possibility that the drug might act as a vitamin analogue, producing nicotinamide deficiency. In this case a deficiency would produce, among other signs, a failure of appetite and a retardation of growth and thereby indirectly affect fat deposition in the liver.

In all experiments, newly weaned 3–4 week old male rats were used. Litter mates were divided between the controls and the test animals. All rats were placed in wire cages with screened bottoms. They were allowed free access to water and diet. Their weights and food intake were recorded daily. The first strain of rats employed suffered a high mortality on the diet and could not be used for this experiment.

[1] Aided by a grant from Mead Johnson and Company, Evansville, Indiana.

Another strain[2] was more satisfactory and was used successfully throughout this study. The basal diet was that of Griffith and Wade (11) and consisted of vitamin free casein 15 parts by weight, crisco 35, sucrose 32, Cox and Imboden's salt mixture (12) 4, calcium carbonate 1, agar 2, cod liver oil 5 and yeast 6. This diet was supplemented with N^1-methylnicotinamide chloride alone or in conjunction with either glycocyamine or nicotinamide. The dosage of glycocyamine varied from 5-10 mM per kilogram of diet, that of N^1-methylnicotinamide from 2–4% (Table I and II) and nicotinamide from 0.4–0.8%. For the sake of simplicity, rats fed a supplemented diet will be referred to as supplemented rats. After a number of weeks on the experiment the animals were killed by chloroform, wet weights of their livers obtained and slices weighing no less than 2.5 grams were taken for fat estimation. Each specimen was individually assayed by continuous chloroform extraction (13) for eight hours. The chloroform fat extracts were evaporated to dryness over a steam bath, then placed in an oven at 110°C. for twenty-four hours and lipid weights obtained.

The effect of N^1-methylnicotinamide on liver lipids of rats fed diet alone

Table I shows the results obtained in three groups of rats, each comprising control animals and animals supplemented with 4% N^1-methylnicotinamide chloride. Group I received the diet for seven days and Group II and III for fourteen and twenty-eight days respectively. There were no deaths during the experiment. The animals were active and behaved normally in every way except that Group I and II showed no gain in weight in the supplemented rats.

There was no difference in the liver lipids between the controls and the supplemented rats of Group I. However, rats in Group II and III, that received the supplemented diet, showed about 4% less fat than the controls.

The effect of N^1-methylnicotinamide on liver lipids of rat fed diet plus glycocyamine

Table II includes the data on five groups of rats in which the control animals ingested the diet supplemented with glycocyamine, whereas

[2] Procured from Research Supply Company, 2436 West York St., Philadelphia, Pa.

the test animals received 2–4% N¹-methylnicotinamide chloride in addition. Glycocyamine, 10 mM per kilogram of diet, was used in all diets except that of Group IV which contained half that amount. The experimental period varied from seven to fourteen days. The animals were active and no deaths occurred.

In contrast to the results in Table I, where no glycocyamine was included in the diet, the liver lipids in these groups were consistently lower in the animals supplemented with the N¹-methylnicotinamide than in the controls. Moreover, the gain in weight in the supplemented animals (except Group VII) were comparable to the controls.

TABLE I

The effect of N¹-methylnicotinamide on liver lipids of rats receiving diet alone

GROUP	DIET SUPPLEMENT N¹-METHYLNICOTINAMIDE CHLORIDE	DURATION OF EXPERIMENT	NO. OF RATS	AGE	AVER. DAILY FOOD INTAKE	AVER. GAIN IN WEIGHT	LIVER FAT % LIVER WEIGHT*	LIVER FAT % BODY WEIGHT	LIVER WEIGHT* % BODY WEIGHT
	gm. %	*days*		*days*	*gm.*	*gm.*			
I	0.0	7	5	21	5.7	11.4	12.6	0.66	5.1
	4.0	7	5	21	5.2	1.0	13.2	0.59	4.4
II	0.0	14	5	21	4.2	9.6	18.2	1.18	6.5
	4.0	14	5	21	3.4	1.4	14.4	0.72	5.0
III	0.0	28	7	21	5.0	30.5	23.1	1.94	8.0
	4.0	28	6	21	4.6	18.0	17.9	1.23	5.8

* Liver weights indicated are wet weights.

The effect of nicotinamide on rats fed diet plus N¹-methylnicotinamide

Three groups of rats were used. Group A consisted of seven rats that ingested the diet alone. Six rats, Group C, were fed diet supplemented with 4% N¹-methylnicotinamide chloride. Seven rats, Group B, received as supplement 4% N¹-methylnicotinamide chloride and 0.4% nicotinamide. On the fourteenth day the nicotinamide was increased to 0.8%. The nicotinamide was used to counteract the possible effect of N¹-methylnicotinamide as an analogue inhibitor.

It is apparent from Figure I that rats of Group A, after an initial loss, gained weight satisfactorily throughout the experiment. How-

TABLE II

The effect of N¹-methylnicotinamide on liver lipids of rats receiving Griffith and Wade diet with glycocyamine

GROUP	DIET SUPPLEMENT		DURATION OF EXPERIMENT	NO. OF RATS	AGE	AVERAGE DAILY FOOD INTAKE	AVERAGE GAIN IN WEIGHT	LIVER FAT % LIVER WEIGHT*	LIVER FAT % BODY WEIGHT	LIVER WEIGHT* % BODY WEIGHT
	N¹-methylnicotinamide chloride	Glycocyamine								
	gm. %	*mM. per kilo*	*days*		*days*	*gm.*	*gm.*			
IV	0.0	5.0	14	9	21	4.9	31.0	12.9	0.64	5.00
	2.0	5.0	14	9	21	4.8	29.5	9.8	0.53	5.10
V	0.0	10.0	7	14	28	4.6	17.0	20.4	1.27	6.13
	2.0	10.0	7	14	28	4.3	10.0	17.5	0.86	4.95
VI	0.0	10.0	14	9	21	4.6	14.0	21.0	1.77	8.19
	2.0	10.0	14	11	21	4.1	10.3	16.9	1.18	7.05
VII	0.0	10.0	7	7	21	4.7	13.8	22.6	1.43	6.38
	4.0	10.0	7	7	21	3.3	3.0	14.8	0.78	5.18
VIII	0.0	10.0	14	7	21	4.3	15.1	29.9	2.55	8.50
	4.0	10.0	14	6	21	4.0	10.6	15.3	0.89	5.87

* Liver weights indicated are wet weights.

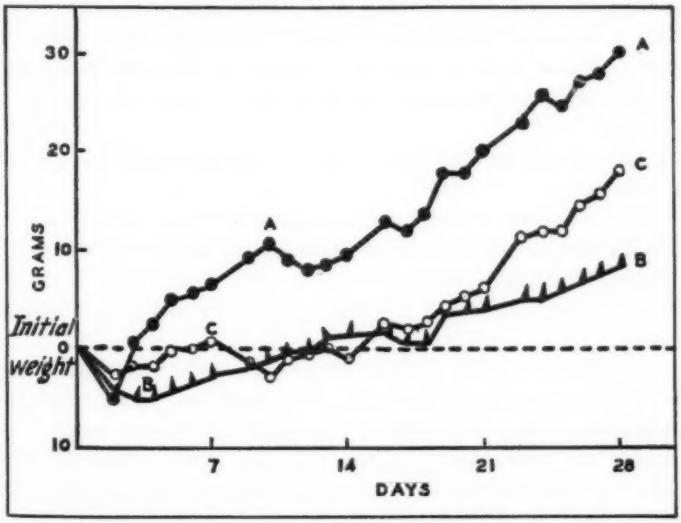

FIG. I. THE AVERAGE DAILY CUMULATIVE WEIGHT GAIN OF RATS RECEIVING DIFFERENT DIETS

A. 7 rats on the basal diet alone. B. 7 rats on the basal diet supplemented with 4% N¹-methylnicotinamide chloride and 0.4% nicotinamide. The latter was increased to 0.8% on the 14th day. C. 6 rats on the basal diet supplemented with 4% N¹-methylnicotinamide chloride.

ever, in Groups B and C, after a similar initial weight loss, there occurred a gain in weight with no significant difference between the two groups though less than Group A. All animals were equally active. It is clear, therefore, that N^1-methylnicotinamide did not possess a vitamin analogue effect which, at least, could be counteracted by nicotinamide.

DISCUSSION

It is clear from the results obtained that the effect of N^1-methylnicotinamide on liver fat, whatever its nature may be, is exerted only to a limited degree under the conditions of our experiment. It appears that the addition of glycocyamine to the diet favored such an effect. This is suggested particularly by the results in Group IV and VIII (Table II). In the former the dietary intake and the gain in weight were almost identical in the supplemented and control animals, although the liver lipids showed a significant difference in favor of the rats receiving the drug. Similarly, in Group VIII the liver fat value of the supplemented rats (15.3%) was much less than the controls (29.9%), although their dietary intake was comparable. It is also apparent that with the increase in the dosage of N^1-methylnicotinamide the effect on liver fat becomes more marked (Table II, Groups VII and VIII).

In attempting to explain our results several possibilities present themselves:

1. That the drug possesses an active labile methyl group. In view of the high dosage used, it is certainly not comparable to that of choline and methionine (14).

2. That the drug has a lipotropic effect without a labile methly group.

3. Another possibility is that the N^1-methylnicotinamide, by competitive action with nicotinamide, precipitated a vitamin deficiency and thereby influenced the fatty deposition in the liver (15, 16, 17). This did not seem likely because the rats were uniformly active. Their food intake did not suggest a loss of appetite and, on the whole, was comparable to the control animals except in two instances—Group II and VII. Furthermore, as shown in Figure I, nicotinamide did not improve the gain in weight nor did the animals receiving N^1-methylnicotinamide reveal any signs of vitamin deficiency.

4. It is also possible that failure of growth may diminish liver fat deposition as suggested by Handler and Bernheim (18). This would be applicable to the N^1-methylnicotinamide treated rats since, in general, they did not gain as well as their respective controls. However, there was a significant difference in the liver fat values in Group IV (Table II) even though the gains in weight of the supplemented and control rats were identical. Conversely, the supplemented rats in Group I (Table I) showed even a higher percentage of fat despite a lack of gain in weight, whereas their controls grew normally.

5. Finally, it is possible that the effect of N^1-methylnicotinamide is a sparing effect similar to that advanced for creatine (19, 20). The diet furnished in our experiment contained methionine and choline so that a sparing effect may be evident. It would also be expected that a sparing action would become more evident when the demand on the methyl group is increased. Such was the case with the glycocyamine supplemented groups where the liver fat of the N^1-methylnicotinamide supplemented rats showed a more significant difference than their controls, as compared to the rats not supplemented with glycocyamine, particularly when 4% of the methyl compound was used.

CONCLUSION

N^1-methylnicotinamide possesses a lipotropic effect, though small in magnitude. The manner in which this action is exerted is, at present, obscure. The different possibilities are discussed.

N^1-methylnicotinamide does not possess an antinicotinamide action and therefore does not enter into competitive inhibition system with the vitamin.

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